Institute of DNA Medicine
Department of Molecular Genetics

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General Summary

The research goal of our department is to develop prophylactic and therapeutic strategies based on disease-specific etiology. Major target diseases are malignant tumors, including hematological and pediatric malignancies. Molecular pharmacological studies of anticancer agents are another area of other research. In particular, we are investigating histone deacetylase inhibitors (HDACIs). We are also investigating the molecular etiology of spinal muscular atrophy (SMA) and retinal diseases.

Research Activities

Exploring leukemogenesis

Several clinical trials for acute leukemias have been performed in the last 2 decades, but except for the treatment of acute promyelocytic leukemia, no protocols have been proven to have a therapeutic advantage over the basic combination chemotherapy proposed in the early 1990s. On the other hand, basic research on leukemia has made extraordinary progress. Leukemic stem cells and the structure of hematopoietic stem cell niche were discovered, and these discoveries have shown why leukemias are resistant to intensive chemotherapies. Megakaryocytic leukemia has an extremely poor prognosis in adult patients. We have recently established a cell line derived from a patient with this disease. This cell line, named JAS-R, show megakaryocyte and erythroblast phenotypes and is ideal for studying the lineage shift between megakaryocytes and erythroblasts. The lineage shift of JAS-R cells is governed by the adherence to culture dishes. Several transcription factors are involved in the lineage determination. Among them, Friend leukemia virus integration 1 (FLI1), a member of the E twenty-six (ETS) gene family, has been shown to play an important role in megakaryocytic differentiation. Therefore, we are now studying the FLI1 induction mechanism along with the cell-adhesion process.

Molecular pharmacology of anticancer agents

Based on the understanding of cancer genomics, many new agents, called molecularly targeted drugs, have been developed. However, the single administration of most new drugs has failed to show a sufficient effect in patients. Thus, combination protocols have been developed. Among the molecularly targeted drugs, HDACIs and their pharmacology have been our focus. Acetylation and deacetylation of histones regulate gene transcription through chromatin remodeling. Transcription genes related to cell survival and death are affected by HDACI treatment. We are studying whether

HDACIs can augment cell cytotoxicity by being administered with conventional anticancer drugs and ionizing radiation. In fact, one HDACI, valproic acid, has shown a synergistic effect with a DNA-topoisomerase I inhibitor. This seems to be a result of induction failure of the antiapoptotic protein B-cell lymphoma 2 extra large (Bcl-xL) by a DNA-topoisomerase I inhibitor. We are also studying the effect of the combination of HDACIs and ionizing radiation against retinoblastoma cells. The dose of radiation to induce apoptosis of cells was reduced to 20% by simultaneous treatment with an HDACI. Unexpectedly, this augmentation was due to the stabilization of a p53-tumor suppressor protein. We are now studying the molecular mechanisms of this stabilization.

Pathogenesis of spinal muscular atrophy

SMA is a degenerative disorder that leads to muscular atrophy. The mutation of the SMA1 gene is responsible for the onset of the disease. However, unlike other mammals, human beings have SMA2, a gene of the same family as SMA1. We are studying why intact SMA2 cannot produce a sufficient amount of SMA protein in patients with SMA.

Publications

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